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ORIGINAL ARTICLE

Evaluation of oral factor Xa inhibitor-associated extracranial bleeding reversal with andexanet alfa

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Abstract

Introduction: A reversal agent for factor Xa (FXa) inhibitors, andexanet alfa, was Food and Drug Administration approved without extensive study of clinical effectiveness, due to an overwhelming demand for FXa inhibitor reversal. In this study, we aimed to describe patient selection, clinical effectiveness, and safety of FXa inhibitor reversal with andexanet alfa in patients presenting with extracranial bleeding.

Methods: Consecutive patients who received andexanet alfa for reversal of FXa inhibitor-associated extracranial hemorrhage were identified. The primary outcome of interest was hemostatic efficacy, assessed using the Sarode et al criteria. Secondary outcomes of interest included incidence of thrombotic episodes post-reversal until discharge and in-hospital mortality.

Results: Twenty-one patients met the inclusion criteria (61.9% male, mean age: 73 years). Anticoagulation reversal with andexanet alfa was deemed effective (excellent [n = 3], good [n = 7]) in 10 (47.6%) patients, and poor in 11 patients (52.4%). Eight (38.1%) patients died, of which three were surgically managed, with all causes of death attributed to hemorrhage. Six ischemic complications occurred in four patients (19.0%); ischemic stroke (n = 2), pulmonary embolism (n = 1), deep vein thrombosis (n = 1), liver ischemia (n = 1), and bowel ischemia (n = 1).

Conclusion: We report poor overall outcomes, a low rate of hemostatic effectiveness, and a high rate of ischemic complications and mortality in this retrospective analysis of oral FXa inhibitor reversal with andexanet alfa for extracranial bleeds. More rigorous epidemiological, and ideally randomized studies, are needed to determine the role of andexanet alfa for FXa inhibitor-associated bleeding for extracranial hemorrhages, where large variation in severity and presentation exists.

KEYWORDS
PRT064445, factor Xa inhibitors, hemorrhage, hemostasis, treatment outcome

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) are increasingly being utilized as alternatives to coumarin derivatives for the treatment and prevention of venous thromboembolism (VTE) as well as prevention of stroke in patients with non-valvular atrial fibrillation, due to improved effectiveness, safety, and cost-effectiveness.[1-8] Additional advantages include more predictable pharmacokinetics/pharmacodynamics, less need for laboratory monitoring, and less drug-drug interactions.[9,10] Uniquely, a potential reversal agent for the factor Xa (FXa) inhibitors, andexanet alfa, was Food and Drug Administration-approved in 2018 without extensive study of clinical effectiveness, due to an overwhelming demand for a specific FXa inhibitor reversal agent.

The available evidence on andexanet effectiveness came from the ANNEXA- A and ANNEXA-R trials, which showed a significant reduction in anti-FXa levels in healthy volunteers anticoagulated with either apixaban or rivaroxaban who were subsequently administered andexanet alfa.[11] The ANNEXA-4 trial was a single-arm, open-label prospective cohort study of clinical effectiveness, and enrolled adult patients presenting with acute major bleeding, defined as potentially life-threatening, bleeding in a critical organ/area, or bleeding associated with a drop in hemoglobin of >2 g/dL.[12] This study found a rate of effective hemostasis of 82% following reversal with andexanet alfa. Potential complications of andexanet alfa reversal are thrombosis, embolism, or ischemic stroke. In the ANNEXA-4 trial, the incidence of thrombotic events was reported to be 10% with a 30-day mortality rate of 14%, and at least 71% of these patients died due to cardiovascular causes.

Reversal with andexanet alfa has not been compared to standard of care or alternative treatment options, such as 4-factor prothrombin complex concentrate (4F-PCC), yet it has become the first-line agent in many institutions and in national organization guidance documents.[13-15] Moreover, the cost of andexanet alfa currently exceeds the national average hospital reimbursement per patient in nearly 75% of patients in the United States.[16] Due to the limited clinical evidence and cost concerns, patient selection for andexanet alfa reversal requires a careful assessment of the patient's hemodynamic stability, time since last dose of FXa inhibitor, the location and severity of bleeding, and the potential effectiveness compared to the incidence of ischemic complications. Patient selection for andexanet alfa reversal in intracranial versus extracranial bleeding is based on different factors, as patient presentation is highly variable. Reversal with andexanet alfa for intracranial hemorrhage at our institutions has been previously described.[17,18] In this study, we aimed to describe patient selection, clinical effectiveness, and safety of oral FXa inhibitor reversal with andexanet alfa in patients presenting with extracranial bleeding.

2 | METHODS

This was a consecutive case series at two large academic level 1 trauma centers (Brigham and Women's Hospital [BWH] and

ESSENTIALS

- Clinical effectiveness of andexanet alfa was not studied extensively prior to FDA approval.
- We report institutional experience with andexanet alfa for extracranial bleeding reversal.
- Hemostatic effectiveness is reported in 47.6% of patients, VTE in 19.0% of patients.
- Rigorous epidemiological studies needed to confirm andexanet alfa's clinical effectiveness.

Massachusetts General Hospital [MGH]) within the same health-care system in Boston, Massachusetts. From January 1, 2018 to December 31, 2019, consecutive adults (≥18 years) who received andexanet alfa for the reversal of oral FXa inhibitor-associated extracranial hemorrhage were identified for inclusion in the study through the institutional pharmacy databases. Andexanet alfa is reserved for patients presenting with acute, life-threatening bleeding per institutional policies Figures 1 and 2. This study was approved by the health-care system Institutional Review Board where the need for informed consent was waived. All data were obtained via manual review of the Epic® (Epic Systems Corporation, Verona, WI, USA) electronic health record. The following data points were collected: age, sex, Charlson comorbidity index, history of VTE, FXa inhibitor and dose, indication for anticoagulation, antiplatelet co-medication, vital signs, anti-FXa levels, base deficit, platelet count (PLT), hematocrit (Hct), hemoglobin (Hgb), lactate, burden of injuries, bleeding site(s), timing of reversal with andexanet alfa, timing of surgery, complications (including re-bleeding and/or ischemic events), intensive care unit (ICU) and hospital length of stay (LOS), in-hospital mortality, and cause of death.

2.1 | Outcomes

The primary outcome of interest was hemostatic effectiveness within 24 hours after bolus infusion, assessed using the criteria set by Sarode et al, and used in the ANNEXA-4 study.[12,19,20] Serial Hct and Hgb values, additional coagulation interventions and transfusion requirement, and objective clinical signs of continued bleeding were collected from the patients' medical records, as well as the timepoints associated with these findings. Thereafter, two authors (CN, LN) independently classified the hemostatic effectiveness for each patient based on the cut-off values set out by Sarode et al, followed by comparison of both authors' assessments. Secondary outcomes of interest were the in-hospital incidence of clinically important thrombotic and ischemic episodes post-reversal, ICU and hospital length of stay, and in-hospital mortality. Ischemic events were reported if they were confirmed on radiographic imaging or by an attending surgeon during a procedure;

Procedures:
1. Criteria for Use:
    a. Andexanet alfa is available for reversal of rivaroxaban or apixaban within 18 hours of the last administered dose in patients with life-threatening or uncontrolled major bleeding as defined by:
        i. Acute (defined as injury insult within 12 hours) CNS, epidural, or ocular bleeding and at high risk of expansion
        ii. Acute CNS or epidural bleeding with expansion on repeat imaging
        iii. Acute exsanguinating hemorrhage being managed operatively with known exposure to rivaroxaban or apixaban
    Note: In patients with active hemorrhage undergoing urgent surgery, andexanet alfa administration should be delayed to facilitate timing of skin incision to occur within 2 minutes of completion of the bolus (at the time of maintenance infusion intitation)
2. Hematology Attending Consult and Approval Required:
    a. Subacute or chronic CNS bleeding (> 12 hours from injury insult)
    b. Acute symptomatic bleeding in a critical organ area with signs or symptoms of hemodynamic compromise
    c. Acute traumatic bleeding managed nonoperatively (e.g. complex pelvic fracture, splenic or liver laceration)
    d. Urgent surgical procedures
    e. Reversal of other anticoagulant therapies targeting Factor-Xa (low molecular weight heparin, edoxaban, betrixaban)
3. Andexanet alfa is not approved for:
    a. Repeated dosing
    b. Surgery that can be delayed
    c. Non-bleeding patients not requiring surgery
    d. Bleeding managed with routine supportive measures
    e. Other anticoagulants
        i. Dabigatran - see Idarucizumab Guideline
        ii. Warfarin - see Fixed dose 4-factor prothrombin complex concentrate Guideline
        iii. Fondaparinux

FIGURE 1 Institutional andexanet alfa patient selection guideline at Massachusetts General Hospital

a "suspected" ischemic event was therefore not included as an ischemic complication.

2.2 | Statistical analysis

Data are presented as mean and standard deviation (SD) or median and interquartile range (IQR), for continuous variables and as number (percentage) for categorical variables. All statistical analyses were performed using STATA® release 15.1 (StataCorp LLC).

3 | RESULTS

Of 77 patients receiving andexanet alfa at this health system between January 1, 2018 and December 31, 2019, 21 patients received the drug for reversal of oral FXa-inhibitor associated extracranial hemorrhage. A brief overview of each patient is provided in Table 1. Patients were mostly male (61.9%) and of geriatric age (mean age of 73 years). Seven patients suffered from acute kidney injury prior to reversal (33.3%), and nine (42.9%) patients suffered from chronic kidney disease. Median estimated glomerular filtration rate (GFR) before reversal was 48 mL/min/1.73 m^2 (IQR 35-83), and GFR was lower than 60 mL/min/1.73 m^2 in 13 (61.9%) patients. Median aspartate aminotransferase before reversal was 27 µL (IQR 18-45), and Median alanine aminotransferase before reversal was 23 µL (IQR 14-46). The median weight at admission was 78 kg [70-96], with 3 patients weighing > 100 kg (14.3%). Median

body mass index (BMI) on admission was 26 kg/m^2 (IQR 22-31). Nine patients (42.9%) had a BMI of>=30 kg/m^2 on admission. The most common indication for anticoagulation was atrial fibrillation (76.2%). Eight patients (38.1%) were treated with concomitant antiplatelet therapy at baseline. Bleeding sources varied, with intra-abdominal (23.8%), gastrointestinal (23.8%), and intrathoracic bleeding (19%) being the most common. Bleeding was visible in five cases (23.8%); three cases of hematemesis, one case of gross hematuria, and one case of melena. Traumatic injury was the cause of bleeding in five patients (23.8%). Most patients presented to the emergency department (ED) after developing symptoms (90.5%), whereas two patients were already admitted to the hospital for elective procedures, after which bleeding complications occurred subsequent to restarting the FXa inhibitor (9.5%). Time between last dose of FXa inhibitor and reversal bolus infusion was unknown in two patients (9.5%). Of the 19 patients (90.5%) with known times since last dose, 16 (16/19; 84.2%) took their last dose within 18 hours of reversal, and over 18 hours in the remaining 3 patients (3/19; 15.8%). The baseline characteristics are presented in Table 2.

On first assessment of potential bleeding, the majority of patients were hemodynamically stable, with only two patients presenting with shock (heart rate > 100 bpm, systolic blood pressure < 100 mmHg). Two patients sustained an out-of-hospital cardiac arrest prior to ED arrival. Nine patients required blood transfusions prior to reversal with andexanet (42.9%), at a median of 4 units (IQR: 4-6 units). The median time between first assessment for potential bleeding and administering andexanet was 106 minutes (IQR: 64.5-194 minutes). Thirteen patients required surgical intervention, one

Currently <u>only</u> approved for the reversal of apixaban and rivaroxaban in the setting of life threatening or uncontrolled major bleeding

All other indications require approval from HAT/Hematology (pager 35287)

Due to the short half-life, limited study population, and rebound in anti-Xa values at 2 hours, this is not currently approved for reversal of apixaban/rivaroxaban for the sole indication of facilitating surgery without concomitant life-threatening bleeding

Criteria	Critical life-threatening bleeding and rivaroxaban/apixaban ingested less than 18 hours ago	Critical life-threatening bleeding	Emergency surgery/procedures **Requires consult with HAT/ Hematology**	Betrixaban Edoxaban Enoxaparin, or Fondaparinux reversal	Less severe bleeding
Indications	For critical life-threatening bleeding defined as bleeding that causes hemodynamic compromise, threatens a vital organ, or may result in disability, that dose not respond to conventional measures and did not receive 4PCC prior	<u>AND</u> dose ingested more than 18 hours ago <u>OR</u> patient received alternative reversal stategies at OSH (eg: 4PCC)	See andexanet surgical flowchart	Not FDA approved, limited data exists	Not approved for less severe bleeding
Approval Required	No approval required for apixabzn or rivaroxaban for critical life-threatening major bleeding if dose less than 18 hr prior	Requires hematology review and approval			Not approved for this use
Laboratory Monitoring	Baseline CBC, Anti-Xa (UFH/LMWH): draw prior to admininistration; do not wait for results	Anti-Xa (UFH/LMWH): Draw immediately for consideration of administration. Recommend sending a start Anti-Xa (LWMH) to check for presence of Fxal drug. If level less than 0.10 no need for reversal; If level between 0.2-1.0 discuss with HAT/Hematology. If level greater than 1.0 give reversal.			Not applicable

If urgent or emergent surgery is required and there is insufficient time to allow the anticoagulant effect to dissipate, HAT service or hematology attending needs to be contacted for siscussion of reversal strategies.

*If greater than 18 hours since last dose, requires STAT anti-factor Xa (LMWH/UFH) level to assess anticoagulant presence before approval of andexanet.

FIGURE 2 Institutional andexanet alfa patient selection guideline at Brigham and Women's Hospital

patient received andexanet alfa 60 minutes after the first incision, time between bolus and incision for the remaining twelve patients was a median of 64 minutes (IQR: 41-195 minutes). The time between bleeding and first incision was < 12 hours for 11 patients (85%). Three patients received the high dose of andexanet alfa (14.3%). Additional coagulation interventions were performed in five patients (23.8%), of which one patient received 4F-PCC directly after the continuous infusion of andexanet alfa was completed, as well as 3 units of FFP and 1 unit of platelets. Four other patients received 1 or more units of FFP. The use of Desmopression (DDAVP), tranexamic acid (TXA), and recombinant factor VII (rFVII) was not reported. An overview of assessment and broad descriptors of treatment are presented in Table 3.

Excellent hemostasis was achieved in three patients, good hemostasis in seven, and poor hemostasis in eleven patients.

Thus, andexanet reversal was deemed effective (ie, excellent [n = 3] or good [n = 7]) in 10 (47.6%) patients. For the remaining 11 patients (52.4%) hemostatic efficacy was deemed poor. Of the 11 patients with poor hemostatic effectiveness, three patients presented with aortic aneurysm or dissection, five presented with intra-abdominal hemorrhage, one presented with upper gastrointestinal hemorrhage, one presented with blunt traumatic hemopneumothorax and retroperitoneal bleeding, and one presented with groin hematoma following a percutaneous procedure. Seven of these patients (64%) underwent surgery, and the mortality rate for patients with poor hemostatic effectiveness was 45% (n = 5/11). Eight patients died (38.1%), all due to hemorrhagic shock; three were surgically managed in addition to use of andexanet alfa. Time to mortality was a median of 1.5 days (IQR 0-10 days) from admission.

TABLE 1 Description of the included patients

Patient (Age, years; Sex)	CCI	Bleeding description	Admission - Reversal (minutes)	Reversal - Incision (minutes)	Surgery performed Post-reversal	Blood Transfusion < 6 Hours Post-Reversal	Hemostatic Effectiveness	In-Hospital Mortality
73F	3	Groin hematoma after percutaneous catheter ablation	79[a]	N/a		2 Units	Poor	0
78M	5	Esophageal perforation	106	61	Right VATS, endoscopy upper GI, exploration neck	0	Excellent	0
72M	3	GSW left abdomen, intra-abdominal hemorrhage	73	~60	Exploratory laparotomy, thoracotomy, distal pancreatectomy, splenectomy, repair of gastric injury, diaphragm repair, splenic flexure takedown	46 Units	Poor	1
53F	1	Subcapsular bleeding	91	30	Exploratory laparotomy, washout	19 Units	Poor	0
83M	7	Hematemesis, arterial extravasation in Whipple surgical bed (26 days prior)	169	>60	Coil embolization of the proximal superior mesenteric artery branch.	0	Poor	0
81M	6	Blunt traumatic hemopneumothorax, retroperitoneal hematoma	66	61	Exploratory laparotomy, right medial visceral rotation, abdominal packing, bilateral internal iliac artery embolization	3 Units	Poor	1
46M	1	Acute on chronic ascending aortic pseudoaneurysm	343	814	Reoperation ascending aortic pseudoaneurysm repair	2 Units	Poor	0
76M	3	Hemopericardium, mass effect in the right atrium and right ventricle with distention of inferior vena cava, retrosternal hematoma	317[a]	81	Mitral valve replacement, amputation left atrial appendage, isolation pulmonary vein, chest irrigation	0	Good	0
63F	4	Intra-abdominal hematoma (5" x 5").	404	N/a		0	Excellent	0
73M	11	Splenic rupture	59	300	Exploratory laparotomy and splenectomy, second look laparotomy, third look laparotomy with bowel resection	10 units	Poor	1
85M	6	Blunt hemothorax	202	N/a		2 units	Good	0
45F	0	Upper gastro-intestinal bleeding	378	>30	Upper GI endoscopy	2 units	Good	0
84M	4	Blunt traumatic prevertebral hematoma	175	1080	C4-T1 Fusion	0	Good	0
69F	8	Cervical epidural hematoma	50	N/a		0	Good	1
90F	9	Traumatic thigh hematoma	131	N/a		2 Units	Good	1
96F	10	Ruptured type B aortic dissection, hemothorax	63	N/a		0	Poor	1

(Continues)

TABLE 1 (Continued)

Patient (Age, years; Sex)	CCI	Bleeding description	Admission - Reversal (minutes)	Reversal - Incision (minutes)	Surgery performed Post-reversal	Blood Transfusion < 6 Hours Post-Reversal	Hemostatic Effectiveness	In-Hospital Mortality
59M	4	Upper GI bleeding	1	>150	Upper GI endoscopy	2 Units	Poor	0
78M	6	Cervical prevertebral hematoma, airway deviation	103	1	Emergent prevertebral hematoma evacuation	0	Excellent	0
88M	10	Retroperitoneal bleed, gross hematuria, bladder perforation	83	N/a		0	Poor	1
95F	11	Type A aortic dissection into pericardium	207	N/a		2 Units	Poor	1
50M	5	Upper GI bleeding	41	>60	Upper GI endoscopy	4 Units	Good	0

Abbreviations: F, female sex; M, male sex; CCI, Charlson Comorbidity Index; GI, gastrointestinal; GSW, gunshot wound; N/a, not applicable; VATS, video-assisted thoracoscopic surgery.

ªThese patients were admitted to hospital prior to initiation of bleeding, time listed indicates time between objective bleeding diagnosis to bolus infusion.

Six ischemic complications occurred in four patients (19.0%); two ischemic strokes (both on day 4), one pulmonary embolism (day 2), one catheter associated right subclavian and axillary vein thrombosis (day 7), one instance of liver ischemia (day 8), and one instance of bowel ischemia (day 8). One patient, who suffered bowel and liver ischemia, received prophylactic heparin per thromboprophylaxis protocol. None of these patients were restarted on DOAC anticoagulation. In patients not developing ischemic complications (n = 17), anticoagulant medication was prescribed in eight (47.1%) patients, at 1 to 4 days post-reversal. Six patients received heparin (four subcutaneous administration, two continuous infusion), one patient received warfarin, and one patient was restarted on apixaban. The indication for DOAC therapy was atrial fibrillation for all four patients who developed ischemic complications, of which one patient had a prior instance of deep venous thrombosis. None of the patients who developed ischemic complications received additional coagulation interventions. The median ICU and hospital LOS were 2 (IQR 0.5-5.5) and 9 (IQR 2.5-11) days, respectively. All outcome measures are presented in Table 4.

4 | DISCUSSION

We found andexanet alfa reversal for FXa inhibitor-associated extracranial bleeding had a lower rate of hemostatic effectiveness compared with previous studies on DOAC-associated bleeding. In prior studies evaluating reversal of FXa inhibitor-associated bleeding with andexanet alfa, hemostatic effectiveness ranged from 57% to 91%, compared to 48% in our cohort.[17,18,20-22] The relatively low rate of hemostatic effectiveness found in our study is potentially explained through differences in patient selection, as patients requiring surgical intervention were excluded in the ANNEXA-4 trial.[20] Moreover, the timing of reversal, as well as surgical and other hemostatic interventions, potentially influenced the hemostatic effectiveness. In our study we report a median 106 minutes between admission and antidote administration, and 64 minutes between antidote administration and surgical intervention on those patients who required it. Both the time to reversal and the time to surgery fall within the ranges of previous studies that reported it.[17,18,22] Considering the short half-lives of FXa inhibitors, a delay in administering andexanet alfa will mean a slight reduction of anti-FXa plasma levels, which also depends on the patient's ability to clear the drug. It remains to be studied if this delay influences the effectiveness of andexanet alfa in this population.

We report a 19% incidence of ischemic complications, which falls within the 0% to 31% range reported in previous andexanet alfa reversal studies.[17,18,20-22] Importantly, andexanet alfa is not a procoagulant agent, but a decoy molecule that temporarily impairs anti-FXa activity. The patient's baseline risk of ischemic complications reconstitutes by withholding anticoagulant medication. It is therefore important to continually assess if it is medically appropriate to restart anticoagulation in the setting of bleeding complications.

TABLE 2 Baseline characteristics of patients who were administered andexanet alfa

Variable name	Result
Number of patients	21
Age, years	73.2 ± 15.4
Male sex	13 (61.9%)
Charlson Comorbity Index	5 (3-8)
Chronic kidney disease	9 (42.9%)
Body mass index in kg/m^2	26 [22-31]
Prior venous thromboembolism	6 (28.6%)
DOAC indication	
Atrial fibrillation	16 (76.2%)
Recurrent popliteal thrombosis post-bypass	1 (4.8%)
Renal thrombosis	1 (4.8%)
Recurrent deep venous thrombosis	1 (4.8%)
Portal vein thrombosis	1 (4.8%)
Superior vena cava occlusion	1 (4.8%)
Factor Xa inhibitor type & dose	
Apixaban 2.5mg twice daily	5 (23.8%)
Apixaban 5mg twice daily	9 (42.9%)
Rivaroxaban 15mg daily	1 (4.8%)
Rivaroxaban 20mg daily	6 (28.6%)
Time since last dose of Factor Xa inhibitor	
<8 hours	5 (23.8%)
8-18 hours	11 (52.4%)
>18 hours	3 (14.3%)
Unknown	2 (9.5%)
Antiplatelet cotherapy	8 (38.1%)
Primary source of bleeding	
Gastrointestinal	5 (23.8%)
Intra-abdominal	5 (23.8%)
Intrathoracic	4 (19.0%)
Retroperitoneal	2 (9.5%)
Prevertebral	2 (9.5%)
Thigh/groin hematoma	2 (9.5%)
Cervical epidural	1 (4.8%)
Visible bleeding	5 (23.8%)
Traumatic injury	5 (23.8%)
Presentation through ED	19 (90.5%)
Bleeding during admission, after DOAC restart	2 (9.5%)

Note: Data presented as median (interquartile range), mean ± standard deviation, or number (percent).

Abbreviations: DOAC, direct acting oral anticoagulant; ED, emergency department.

Designing clinical guidelines for use of andexanet alfa is particularly challenging, given the paucity of clinical evidence on its effectiveness and safety. Further difficulty arises from the inability to ascertain the degree of oral FXa inhibitor-exposure in a timely and accurate manner, as the time since last oral FXa administration is often unknown and apixaban- and rivaroxaban-specific anti-FXa assays may not be available or processed immediately by an institution's laboratory. At one of our institutions, cut-off points were determined to allow for rapid decision making by front line clinicians. Using a heparin-calibrated anti-FXa assay, levels of < 0.1 IU/mL were interpreted as clinically irrelevant levels of Xa inhibitor, whereas for levels > 1.0 IU/mL a reasonable impact of FXa inhibitors on bleeding was to be expected, and reversal agents could be used.[23,24] For values in between, a hematology consult was required, as factors such as renal function and time since last dose should be weighed by an expert provider. Comorbidities and frailty of patients with FXa inhibitor-associated bleeding may additionally impact the efficacy and safety of andexanet alfa therapy; however, this association could not be confirmed in our study. Furthermore, ethical and economic considerations should be considered, which are not addressed in this article.

The prescribing information published by the manufacturer (Portola Pharmaceuticals, Inc, South San Francisco, CA, USA) specify that life-threatening or uncontrolled bleeding constitutes an appropriate indication to prescribe andexanet alfa. The MGH protocol further stipulates life-threatening bleeding in three specific bleeding sites or to exsanguinating hemorrhage warranting surgical intervention (Figure 1). Indications not specifically mentioned in the MGH protocol require hematology consult and approval. Clinician judgment of what constitutes life-threatening bleeding forms the basis for patient selection at BWH and other centers that described their protocol, which more closely mirror the prescribing information published by the manufacturer (Figure 2).[17,21,22] All discussed protocols stated that indications not specified in the protocol may qualify for use of andexanet alfa after hematology or pharmacy consult and approval.

Another argument surrounding the use of andexanet alfa for FXa inhibitor-associated bleeding is whether it is superior to 4F-PCC, which has been utilized and studied more widely in clinical practice as a potential reversal agent for the FXa inhibitors. Considering the paucity of data and the high baseline risk of poor outcome and complications in this patient population, comparative studies of andexanet alfa and other reversal agents or usual care are urgently needed. To our knowledge, there has been one head-to-head comparison of these two reversal strategies, but statistical analysis was not performed to compare effectiveness due to a limited sample size.[18] A plethora of single-arm cohort studies of 4F-PCC reversal for FXa-associated bleeding have reported effectiveness rates of 69%-95%, defined using the Sarode et al criteria or significant intracranial hemorrhage progression.[25-32] The Sarode et al criteria were also used by most studies on real-world use of andexanet alfa reversal.[18-22] However, these criteria require standardized patient selection to be able to compare the hemostatic effectiveness of andexanet and 4F-PCC, as selection bias is present otherwise.

Quantifying the reduction in anti-FXa activity in blood was used as the outcome to register andexanet alfa as a reversal agent.[11] The

TABLE 3 Assessment and treatment modalities

Variable name	N	Result
First assessment for potential bleeding		
Baseline anti factor Xa level in U/mL	2	1.88; 3.80
Systolic blood pressure in mmHg	21	127 (96-136.5)
Pulse rate in bpm	21	92 (69.5-99.5)
Temperature in C°	17	36.7 (36.4-37.1)
Oxygen saturation %	17	97 (96-98)
Glasgow Coma Scale	17	15 (15-15)
Hemoglobin in g/dL	20	10.4 (8.6-13.2)
Hematocrit %	20	33.0 (27.6- 41.1)
Platelet count in K/uL (IQR)	17	183 (141-231)
International normalized ratio (IQR)	18	1.45 (1.2-2.2)
Base deficit mEq/L	7	6.4 (1.1-8.0)
Lactate in mmol/L	14	3.65 (1.8-8.7)
Estimated glomerular filtration rate in mL/min/1.73m^2	20	48 [35-83]
Aspartate aminotransferase in U/L	20	27 [18-45]
Alanine aminotransferase in U/L	20	23 [14-46]
Pre-hospital cardiac arrest	21	2 (9.5%)
Pre-reversal acute kidney injury	21	7 (33.3%)
Minutes spent in Emergency Department	21	247 (123.5-397.5)
Transfusion need pre-reversal	21	9 (42.9%)
Volume in units	9	4 (4-6)
Minutes from bleeding to reversal bolus Administration	21	106 (64.5-194)
Andexanet dose		
High: 800 bolus followed by 880 mg infusion over 2 hours	21	3 (14.3%)
Low: 400 bolus followed by 480 mg infusion over 2 hours	21	18 (85.7%)
Underwent surgery	21	13 (61.9%)
Bolus before surgery start	13	12 (57.1%)
Minutes from reversal bolus to incision	12	64 (41-195)
Bolus after surgery start	13	1 (4.8%)
Minutes delay	1	60
Interventional radiology procedure	21	1 (4.8%)
Additional hemodynamic measures post-reversal	21	15 (71.4%)
Vasopressors 1-hour post-reversal	21	8 (38.1%)
4-factor prothrombin complex concentrate	21	1 (4.8%)
Blood transfusion	21	12 (57.1%)
Median units transfused 6-hours post-reversal	12	2 (2-4.5)
Angio-embolization	21	2 (9.5%)

Note: Data presented as median (interquartile range) or number (percent).

TABLE 4 Primary and secondary outcomes

Variable	N	Result
Hemostatic effectiveness at 24 hours		
Excellent	21	3 (14.3%)
Good	21	7 (33.3%)
Poor	21	11 (52.4%)
In-hospital mortality	21	8 (38.1%)
Bleeding-related	21	8 (38.1%)
Time to in-hospital mortality, days	8	1.5 (0-10)
Patients with>=1 ischemic complication	21	4 (19.0%)
Stroke	21	2 (9.5%)
Pulmonary embolism	21	1 (4.8%)
Deep venous thrombosis	21	1 (4.8%)
Bowel ischemia	21	1 (4.8%)
Liver ischemia	21	1 (4.8%)
ICU length of stay, days	16	2 (1.5-6.5)
Hospital length of stay, days	21	9 (2.5-11)

Note: Data presented as median (interquartile range) or number (percent).

ANNEXA-4 trial demonstrated that a reduction in anti-FXa activity in blood correlates poorly to hemostatic effectiveness in extracranial bleeding.[20] In our cohort, pre- and post-reversal drug-specific anti-FXa levels were not routinely ordered, nor were they reported in the other real-world studies of andexanet alfa reversal.[17,18,21,22] Moreover, results of the rivaroxaban and apixaban-anti-FXa assays may not be available until after the time window in which decisions must be made concerning management of life-threatening bleeding, limiting their clinical applicability. Considering the yet unknown cost-effectiveness of both reversal strategies, prospective randomized studies are needed to determine the position of 4F-PCC and andexanet alfa within management protocols for FXa inhibitor-associated bleeding for both intracranial and extracranial bleeding.

This study has several limitations. First, its retrospective design and the heterogeneity of the described patient population impeded matching of an appropriate comparison group of patients reversed with 4F-PCC, or those for whom andexanet was considered but not administered. The retrospective design also limited our ability to determine the rationale for the use of andexanet alfa. Despite detailed prescribing documents, selection bias is present in this study. Therefore, the hemostatic effectiveness found in our study potentially reflects prescribing practice at our institutions, and not necessarily a generalizable effectiveness of andexanet alfa. Second, retrospective collection of data introduces risk of bias in reporting outcomes. However, due to the clear variables and cut-off values at predetermined time-points used in determining hemostatic efficacy, and the available imaging and progress reports for ischemic events, we expect the influence of outcome reporting bias to be limited. Third, the use of a 24-hour timeframe

potentially influenced our results. The Sarode et al criteria consider a 24-hour timeframe, whereas the ANNEXA-4 study measured hemostatic effectiveness at 12 hours.[19,20] Normalization of Hgb and Hct is expected to occur more often during a 24-hour window, compared to a 12-hour window, whereas the incidence of continued bleeding or re-bleeding and associated interventions is to be expected more often during a 24-hour window. Weighing these outcomes, we expect that hemostatic effectiveness measured using a 24-hour timeframe will be slightly higher, compared to using a 12-hour timeframe. Fourth, our study is limited by sample size, which does not allow for statistical testing of hypotheses, and risks over- and underestimation of true ischemic event rates. Caution in interpretation of our results is advised as further experience with andexanet alfa in larger cohorts will increase our understanding of the effectiveness and risks. Last, differences in the prescribing guidelines for andexanet alfa existed between the participating hospitals. However, because no comparison was performed, the impact of these differences is limited. Based on our institutional experience, we intend to continue our prescribing practice, while continually evaluating individual patient outcomes, and published data of more rigorous, ideally randomized studies to refine our guidelines and practice.

5 | CONCLUSION

Experience with andexanet alfa reversal for FXa inhibitor-associated extracranial bleeding in an urban, academic health system indicates poor overall outcome and a low rate of hemostatic effectiveness, but similarly high rates of ischemic complications and mortality compared with previously published data. Use of andexanet alfa must be controlled and monitored using strict guidelines for use and updated as more data on (cost-)effectiveness and safety becomes available. More rigorous epidemiological, and ideally randomized, studies are needed to determine the role of andexanet alfa within management protocols for FXa inhibitor-associated bleeding for all indications, but especially extracranial bleeding for which more variation in severity and presentation exists.

CONFLICTS OF INTEREST

C. J. Nederpelt, L. Naar, M. E. Barra, K. W. Sylvester, R. J. Roberts, G. C. Velmahos, H. M. A. Kaafarani, M. G. Rosenthal, and D. R. King declare no conflicts of interest pertaining to the topic of this research. K. W. Sylvester reports consulting for Portola Pharmaceuticals and serving on an advisory board for Bristol Meyers Squibb – Pfizer. No funding was obtained to perform this research.

AUTHOR CONTRIBUTIONS

C. J. Nederpelt, M. G. Rosenthal, and D. R. King were involved in study conception and design. C. J. Nederpelt, L. Naar, M. E. Barra, and K. W. Sylvester collected the data. All authors were involved in results interpretation. C. J. Nederpelt and L. Naar wrote the manuscript. All authors reviewed the manuscript.

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